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Specification

NOVEL QUINUCLIDINE DERIVATIVES AND MEDICINAL
COMPOSITION THEREOF

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Technical Field

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This invention relates to medicines, particularly quinuclidine derivatives or their salts, ~~N-oxides~~ or quaternary ammonium salts having muscarinic receptor antagonistic activities and also to pharmaceutical compositions containing such compounds.

Background Art

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Studies have been made on the muscarinic receptor, and it is known that compounds having muscarinic receptor antagonistic activities cause bronchodilation, suppression of gastrointestinal motility, suppression of acid secretion, dry mouth, mydriasis, suppression of bladder contraction, hypohidrosis, tachycardia, or the like. It is known that the muscarinic receptor includes at least three subtypes. The M₁ receptor mainly exists in the brain or the like, the M₂ receptor in the heart or the like, and the M₃ receptor in the smooth muscles or gland tissues.

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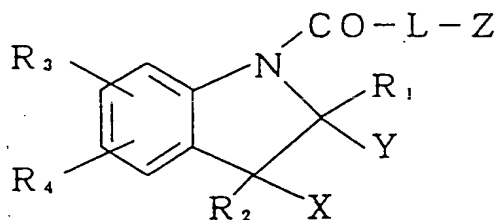
A number of such compounds having muscarinic receptor antagonistic activities are hitherto known and, for example, atropine is a typical example ("The MERCK INDEX, ELEVENTH EDITION", p. 138). However, atropine antagonizes the M₁, M₂

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and M₃ receptors non-selectively, so that it is difficult to use it for the treatment of a specific disease. In recent years, according to the progress of the studies on the subtypes of the muscarinic receptor, compounds having selective antagonistic activities against the M₁, M₂ or M₃ receptor have been investigated (an unexamined published British Patent Application No. -2,249,093, an unexamined published Japanese Patent Application (*kokai*) 1-131145, and an unexamined published Japanese Patent Application (*kokai*) 3-133980). There is a demand for a compound having selective antagonistic activity against muscarinic M₃ receptor among these three subtypes and is free from the cardiac side effects resulting from the M₂ receptor.

The compound represented by the following general formula is described in an unexamined published Japanese Patent Application (*kokai*) 62-252764.



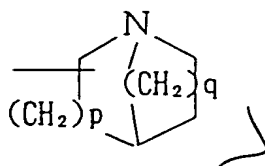
(wherein L represents NH or O;

X and Y each independently represents a hydrogen atom or a C₁₋₆ alkyl group or they may be combined together to form a bond;

R₁ and R₂ each independently represents a hydrogen atom, a C₁₋₆ alkyl group ... (omission) ... ;

R₃ and R₄ each independently represents a hydrogen atom, a halogen atom, CF₃, a C₁₋₆ alkyl group ... (omission) ..., a phenyl group, an amino group which may optionally be N-substituted by one or two groups selected from phenyl, C₁₋₆ alkyl groups or may optionally be N-disubstituted by C₆₋₈ polyethylene... (omission) ...;

Z represents



or the like;

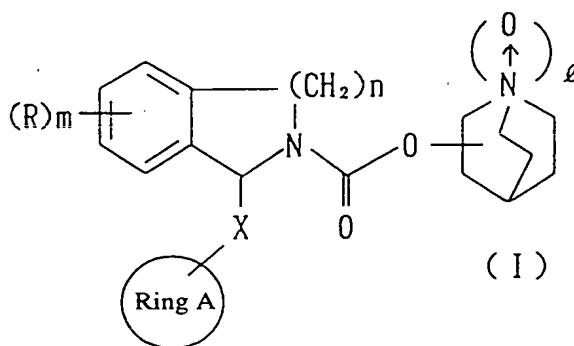
p is 1 or 2; and q is 1-3.

The compound described in the above patent literature is disclosed as a 5-HT antagonist and no disclosure about the muscarinic receptor antagonistic activity is found. The above compound is clearly distinguished from the compound according to the present invention in pharmacological effects.

Disclosure of the Invention

The inventors of the present application have carried out extensive studies on compounds having the above-described muscarinic M₃ receptor antagonistic activities. As a result, we created novel quinuclidine derivatives having a basic skeleton different from that of the conventional compound, and found that such compounds have excellent selective antagonistic activity against muscarinic M₃ receptor, resulting in the completion of the present invention.

Thus, the compounds of the present invention relate to quinuclidine derivatives represented by the following general formula (I); their salts, ~~N-oxides~~ or quaternary ammonium salts; pharmaceutical compositions comprising said compounds or salts thereof and pharmaceutically acceptable carriers, particularly to muscarinic M₃ receptor antagonists.



(symbols in the formula have the following meanings:

Ring A: an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, wherein said ring may be substituted by an optional substituent;

X: a single bond or a methylene group;

R: a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group or a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group;

l: 0 or 1,

m: 0 or an integer of 1 to 3, and

n: an integer of 1 or 2, hereinafter the same apply similarly)

Among the compound (I) of the present invention, particularly preferred compounds are quinuclidine derivatives wherein the ring A represents an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, in which such a ring may be substituted by a substituent selected from the group consisting of a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group, and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group, and their salts, ~~N-oxides~~ or quaternary ammonium salts;

quinuclidine derivatives wherein R represents a halogen atom, a lower alkyl group, a hydroxyl group, a lower

alkoxy group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group, and the ring A represents an aryl group, a cycloalkyl group, a cycloalkenyl group, a 5- or 6-membered monocyclic heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, in which such a ring may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group or a mono- or di-lower alkylamino group, and their salts, ~~N-oxides~~ or quaternary ammonium salts;

quinuclidine derivatives wherein m is 0, and the ring A represents an aryl group, a cycloalkyl group or a cycloalkenyl group which may be substituted by a halogen atom, a lower alkyl group, a hydroxyl group or a lower alkoxy group, or a 5- or 6-membered monocyclic heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom, and their salts, ~~N-oxides~~ or quaternary ammonium salts;

quinuclidine derivatives wherein the ring A represents a phenyl group which may be substituted by a halogen atom or a lower alkyl group, a cycloalkyl group, a pyridyl group, a furyl group or a thienyl group, and their salts, ~~N-oxides~~ or quaternary ammonium salts;

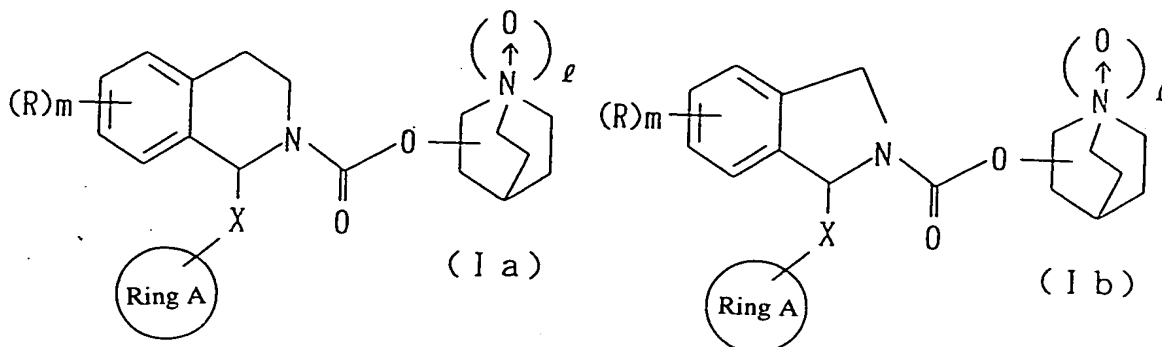
quinuclidine derivatives wherein X represents a single bond, and their salts, ~~N-oxides~~ or quaternary ammonium salts; and

quinuclidine derivatives wherein n is 2, and their salts, ~~N-oxides~~ or quaternary ammonium salts.

The present invention also provides muscarinic M₃ receptor antagonists which comprise quinuclidine derivatives (I) or their salts, ~~N-oxides~~ or quaternary ammonium salts, that is, the compound (I) of the present invention and pharmaceutically acceptable carriers, preferably agents for the prevention and/or treatment of urinary diseases (e.g., neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis), or respiratory diseases (e.g., chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis).

Hereinafter, the compound (I) of the present invention will be described in detail.

Different from the conventional muscarinic M₃ receptor antagonist, the compound (I) of the present invention is structurally characterized in that it has as a basic skeleton a tetrahydroisoquinoline skeleton (Ia) or isoindoline skeleton (Ib) having a quinuclidinyloxycarbonyl group, etc. bonded to the nitrogen atom in the ring as shown below.



10 Furthermore, the compound (I) of the present invention is characterized in that it has ring A, that is, a cyclic group selected from an aryl group, a cycloalkyl group, a cycloalkenyl group, a heteroaryl group having 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom or a 5- to 7-membered saturated heterocyclic group, at the 1-position of the tetrahydroisoquinoline or isoindoline through X.

15 Unless otherwise specified, the term "lower" as used in the definition of the general formula in this specification means a linear or branched carbon chain having 1 to 6 carbon atoms. Accordingly, the "lower alkyl group" means linear or branched alkyl group having 1 to 6 carbon atoms. Specific examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl,

1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl,
1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl,
1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-
trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-

5 methylpropyl groups. Among these groups, alkyl groups having
1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl
and butyl groups are preferred, and a methyl group is more
preferred.

10 The "aryl group" means aromatic hydrocarbon groups
and preferably aryl groups having 6 to 14 carbon atoms.
Specific examples include phenyl, naphthyl, indenyl, anthryl
and phenanthryl groups, and a phenyl group is more preferred.

15 Examples of the "cycloalkyl group" include those
having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Among
these groups, cyclopropyl, cyclobutyl, cyclopentyl and
cyclohexyl groups are preferred, and a cyclohexyl group is
more preferred.

20 Examples of the "cycloalkenyl group" include those
having 3 to 8 carbon atoms such as 1-cyclopropenyl,
2-cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl,
1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl,
1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl,
1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl,
25 4-cycloheptenyl, 1-cyclooctenyl, 2-cyclooctenyl,
3-cyclooctenyl, 4-cyclooctenyl, 2,4-cyclopentadienyl,

2,5-cyclohexadienyl, 2,4-cycloheptadienyl, and
2,6-cycloheptadienyl.

5 The "heteroaryl group containing 1 to 4 hetero atoms
selected from the group consisting of an oxygen atom, a
nitrogen atom and a sulfur atom" means a 5- or 6-membered
heteroaryl group which may be condensed with a benzene ring.
Specific examples include 5- or 6-membered monocyclic
heteroaryl groups containing 1 to 4 hetero atoms selected
from the group consisting of an oxygen atom, a nitrogen atom
and a sulfur atom, such as furyl, thienyl, pyrrolyl,
10 imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isothiazolyl,
isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl
groups; and 5- or 6-membered heteroaryl groups condensed with
a benzene ring, such as indolyl, indazolyl, indolizinyl,
15 quinolyl, quinazolinyl, quinolizinyl, quinoxalinyl,
cinnolinyl, benzimidazolyl, benzofuranyl,
dihydrobenzofuranyl, benzoisoxazolyl, benzooxazolyl,
benzothiazolyl and benzothienyl groups.

20 Among these groups, preferred are 5- or 6-membered
monocyclic heteroaryl groups containing 1 to 4 hetero atoms
selected from the group consisting of an oxygen atom, a
nitrogen atom and a sulfur atom, and furyl, thienyl and
pyridyl groups are more preferred.

25 The "5- to 7-membered saturated heterocyclic group"
means a 5-, 6- or 7-membered saturated heterocyclic group
containing 1 to 2 oxygen, nitrogen and/or sulfur atoms.

Specific examples include pyrrolidinyl, imidazolydiny, piperidinyl, piperazinyl and morpholinyl groups.

The "aryl group", "cycloalkyl group", "cycloalkenyl group", "heteroaryl group containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom", "5- or 6-membered monocyclic heteroaryl group containing 1 to 4 hetero atoms selected from the group consisting of an oxygen atom, a nitrogen atom and a sulfur atom", or "5- to 7-membered saturated heterocyclic group" as the group A may be substituted by an optional substituent. The number of the substituent is not limited to one but may be plural. Any group that can substitute for such a ring can be employed as the optional substituent. Preferred examples include a halogen atom, a hydroxyl group, a lower alkoxy group, a carboxyl group, a lower alkoxycarbonyl group, a lower acyl group, a mercapto group, a lower alkylthio group, a sulfonyl group, a lower alkylsulfonyl group, a sulfinyl group, a lower alkylsulfinyl group, a sulfonamido group, a lower alkanesulfonamido group, a carbamoyl group, a thiocarbamoyl group, a mono- or di-lower alkylcarbamoyl group, a nitro group, a cyano group, an amino group, a mono- or di-lower alkylamino group, a methylenedioxy group, an ethylenedioxy group and a lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group; a

halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, a cyano group, an amino group and a mono- or di-lower alkylamino group are more preferred; a halogen atom, a lower alkyl group, a hydroxyl group and a lower alkoxy group are still more preferred; and a halogen atom and a lower alkyl group are particularly preferred.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine. When the substituent is a halogen atom, the number of the substituents is not particularly limited. When two or more halogen atoms are substituted, any combination of the above atoms is possible. Examples of the halogen atom-substituted lower alkyl group include fluoromethyl, chloromethyl, bromomethyl, iodomethyl, 1-fluoroethyl, 1-chloroethyl, 1-bromoethyl, 2-chloroethyl, 2-bromoethyl, dichloromethyl, trifluoromethyl, trichloromethyl, tribromomethyl, triiodomethyl and dichlorobromomethyl. Among these groups, a trifluoromethyl group is preferred.

Examples of the "lower alkoxy group" include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy (amyloxy), isopentyloxy, tert-pentyloxy, neopentyloxy, 2-methylbutoxy, 1,2-dimethylpropoxy, 1-ethylpropoxy and hexyloxy. Among these groups, lower alkoxy groups containing an alkyl group having 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy and butoxy are preferred, and methoxy and ethoxy groups are more preferred.

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Examples of the lower alkoxy carbonyl group include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 5 pentyloxy(amyloxy)carbonyl, isopentyloxycarbonyl, tert-pentyloxycarbonyl, neopentyloxycarbonyl, 2-methylbutoxycarbonyl, 1,2-dimethylpropoxycarbonyl, 1-ethylpropoxycarbonyl and hexyloxycarbonyl.

Examples of the "lower acyl group" include formyl, 10 acetyl, propionyl, butyryl, valeryl and pivaloyl, and formyl, acetyl and propionyl are preferred.

The "lower alkylthio group" means a mercapto group of which hydrogen atom has been substituted by the above- 15 exemplified lower alkyl group, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio and hexylthio groups.

Examples of the "lower alkylsulfonyl group" include 20 methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, pentylsulfonyl and hexylsulfonyl.

Examples of the "lower alkylsulfinyl group" include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl and 25 hexylsulfinyl.

Examples of the "lower alkanesulfonamido group" include methanesulfonamido, ethanesulfonamido,

propanesulfonamido, isopropanesulfonamido, butanesulfonamido, pentanesulfonamido and hexanesulfonamido.

5 The "mono- or di-lower alkylcarbamoyl group" means a carbamoyl group in which one or two hydrogen atom(s) have been substituted by the above-exemplified lower alkyl group(s), such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl and dimethylcarbamoyl groups.

10 The "mono- or di-lower alkylamino group" means an amino group in which one or two hydrogen atom(s) have been substituted by the above-exemplified lower alkyl group(s), such as methylamino, ethylamino, propylamino, dimethylamino, diethylamino and dipropylamino groups.

15 The term "lower alkyl group which may be substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group" means a lower alkyl group in which at least one optional hydrogen atom has been substituted by a halogen atom, a hydroxyl group, a lower alkoxy group, an amino group or a mono- or di-lower alkylamino group. The lower alkyl group substituted by
20 a halogen atom is as described in the above description of the halogen atom.

The compound (I) of the present invention contains a quinuclidinyl group. The nitrogen atom of the quinuclidinyl group may form oxide ($\ell = 1$) or quaternary ammonium salt.

25 Where a quaternary ammonium salt is formed, specific examples

of the group bound to the nitrogen atom include lower alkyl, lower alkenyl and lower alkynyl.

5 The term "lower alkenyl" as used herein means a linear or branched alkenyl group having 2 to 6 carbon atoms, such as vinyl, propenyl, butenyl, methylpropenyl, dimethylvinyl, pentenyl, methylbutenyl, dimethylpropenyl, ethylpropenyl, hexenyl, dimethylbutenyl and methylpentenyl. Among these groups, a propenyl group is preferred.

10 The "lower alkynyl group" means a linear or branched alkynyl group having 2 to 6 carbon atoms, such as ethynyl, propynyl, butynyl, methylpropynyl, pentynyl, methylbutynyl and hexynyl groups. Among these groups, alkynyl groups having 2 to 3 carbon atoms such as ethynyl and propynyl are preferred.

15 The anion for the quaternary ammonium salt is not particularly limited and the examples include ions of a halogen atom, triflate, tosylate and mesylate, preferably ions of a halogen atom, i.e. halide ions (e.g., chloride ion, bromide ion, iodide ion and triiodide ion). Examples of
20 other anions include inorganic anions such as nitrate ion, sulfate ion, phosphate ion and carbonate ion, carboxylates such as formate (HCOO^-), acetate (CH_3COO^-), propionate, oxalate and malonate, and amino acid anions such as glutamate. Among the halide ions, bromide ion and iodide ion
25 are preferred. Incidentally, the anion can be converted into

a preferable anion as needed by the ordinary ion exchange reaction.

5 The compound (I) of the present invention contains an asymmetric carbon atom so that there exist optical isomers based on it. In addition, some of the invention compounds have stereoisomers or tautomers. The present invention also embraces diastereomers and enantiomers obtained by the separation of the above isomers as well as mixtures thereof.

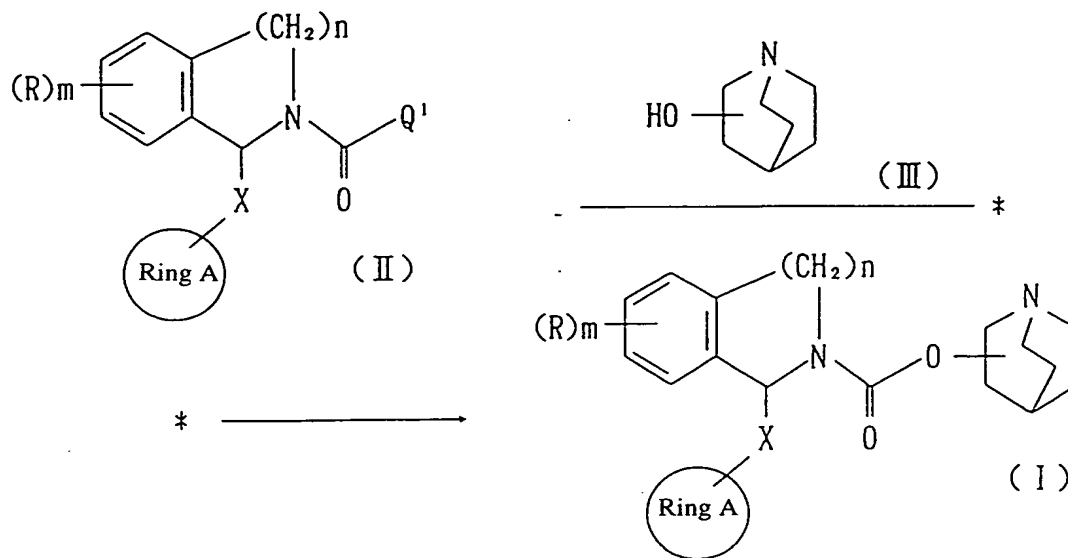
10 Some of the compounds (I) of the present invention can form salts with an acid as well as the above-described quaternary ammonium salts with a quinuclidynyl group. Examples of such salt include acid addition salts with a mineral acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid or phosphoric acid; and those with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethanesulfonic acid or glutamic acid.

15 20 The compounds (I) of the present invention also embrace hydrates, solvates with ethanol or the like, and substances in any polymorphism crystals.

(Preparation Process)

25 The compound (I) of the present invention can be prepared in accordance with various processes. The typical preparation processes are explained below.

First preparation method



(in the formula, Q^1 represents a leaving group which is advantageous in the present reaction, and ring A, R, X, m and n have the same meanings as defined above. Hereinafter, the same will apply similarly).

This reaction is carried out by stirring the compound represented by the general formula (II) and quinuclidinol represented by the general formula (III) in an amount corresponding to the reaction in an inert solvent at room temperature or under heating.

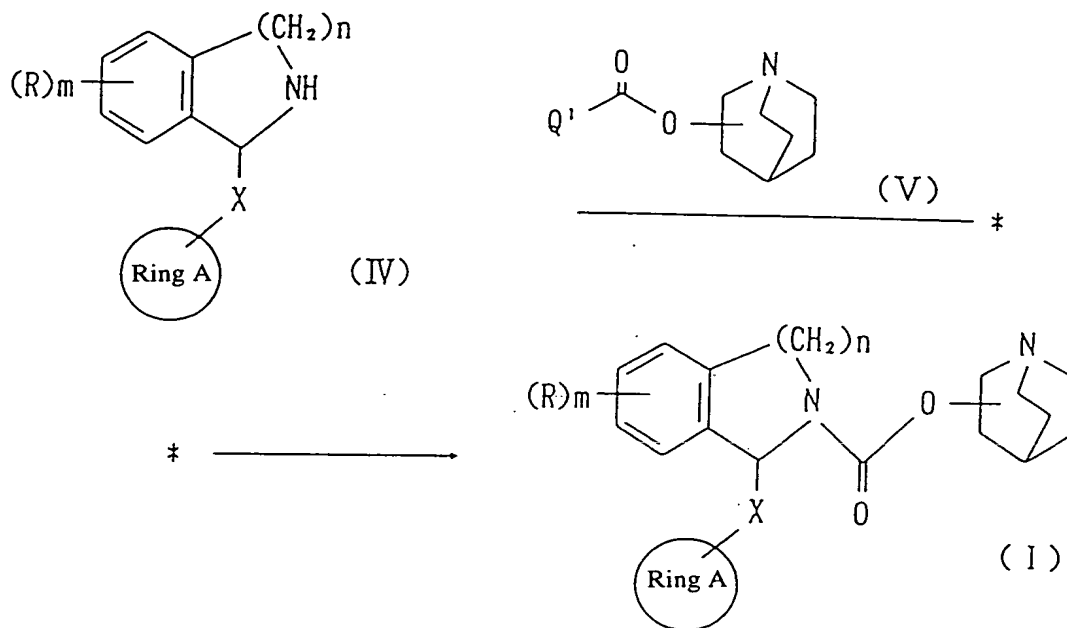
The leaving group Q^1 embraces, for example, a halogen atom, a lower alkoxy group, a phenoxy group and an imidazolyl group.

Examples of the inert solvent include

5 dimethylformamide (DMF), dimethylacetamide, tetrahydrofuran (THF), dioxane, dimethoxyethane, diethoxyethane, benzene, toluene and xylene and mixed solvents thereof.

It is preferable to add a base (e.g., sodium, sodium hydride, sodium methoxide and sodium ethoxide) in order to accelerate the present reaction.

Second preparation method



25 (wherein the ring A, R, X, m, n and Q^1 have the same meanings as defined above.)

This reaction is carried out by stirring the compound represented by the general formula (IV) and the compound represented by the general formula (V) in the above-described inert solvent at room temperature or under heating.

5 It is preferable to add a base (e.g., sodium, sodium hydride, sodium methoxide, sodium ethoxide, triethylamine and pyridine) in order to accelerate the present reaction. (Other preparation methods)

10 Among the compounds of the present invention, a compound in which the nitrogen atom of the quinuclidinyl group forms oxide or a quaternary ammonium salt can be prepared by N-oxide formation or N-alkylation of a tertiary amine compound in the compounds of the present invention.

15 The N-oxide formation reaction can be carried out by the oxidation reaction in a conventional manner, more specifically, by stirring a tertiary amine compound in the compounds of the present invention and a corresponding amount or excess amount of oxidizing agent in an inert solvent such as chloroform, dichloromethane or dichloroethane, an alcohol such as methanol or ethanol or water or a mixed solvent
20 thereof under cooling or at room temperature, or in some cases under heating. Examples of the oxidizing agent include organic peracids such as m-chloroperbenzoic acid, sodium periodate and hydrogen peroxide.

25 The N-alkylation reaction can be carried out in accordance with the conventional N-alkylation reaction, more

specifically by stirring a tertiary amine compound in the compound of the present invention and a corresponding amount of an alkylating agent in an inert solvent such as dimethylformamide, chloroform, benzene, 2-butanone, acetone or tetrahydrofuran under cooling or a room temperature, or in some cases under heating.

Examples of the alkylating agent include lower alkyl halides, lower alkyl trifluoromethanesulfonates, lower alkyl p-toluenesulfonates and lower alkyl methanesulfonates, preferably lower alkyl halides.

For the preparation of the compound of the present invention, it is sometimes necessary to protect a functional group. In such a case, introduction of a proper protecting group and deprotection operation in a conventional manner are carried out additionally.

The compound of the present invention so prepared is provided as is in the free form, or after subjected to the salt formation treatment in a conventional manner, it is isolated and purified as its salt. Isolation and purification are carried out by the ordinary chemical operation such as extraction, concentration, evaporation, crystallization, filtration, recrystallization or a variety of chromatography.

Industrial Applicability

5 The compound of the present invention has affinity and selectivity for the muscarinic M_3 receptor and, as an M_3 receptor antagonist, it is useful as an agent for prevention or treatment of various M_3 receptor-related diseases, particularly urinary diseases such as urinary incontinence or pollakiuria in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm or chronic cystitis; respiratory diseases such as chronic obstructive pulmonary diseases, chronic bronchitis, asthma or rhinitis; or digestive diseases such as irritable bowel syndrome, spastic colitis or diverticulitis.

10 In particular, the compound of the present invention has high selectivity for the M_3 receptor existing in the smooth muscle or gland tissues compared with the M_2 receptor existing in the heart or the like, so that it has high utility as an M_3 receptor antagonist having less side effects on the heart or the like, particularly as an agent for prevention or treatment of urinary incontinence, pollakiuria, chronic obstructive pulmonary diseases, chronic bronchitis, asthma or rhinitis.

20 The affinity and antagonism of the compound of the present invention for the muscarinic receptor was confirmed by the following tests.

8 Muscarinic receptor ^{binding} ~~affinity~~ test (*in vitro*)

a. Preparation of membranes

5 From a male Wistar rat (Japan SLC), the heart and submandibular gland were excised, mixed with a 20 mM HEPES buffer (pH 7.5, which will hereinafter be abbreviated as "HEPES buffer") containing 5 times the volume of 100 mM sodium chloride and 10 mM magnesium chloride was added, followed by homogenization under ice-cooling. The resulting mixture was filtered through gauze, followed by ultracentrifugation at 50,000 × g and 4°C for 10 minutes. The precipitate obtained was suspended in an HEPES buffer, followed by further ultracentrifugation at 50,000 × g and 4°C for 10 minutes. The precipitate obtained was suspended in an HEPES buffer. The resulting suspension was stored at -80°C and provided for the test after melting upon use.

b. Muscarinic M₂ receptor binding test

15 The test was carried out in accordance with the method of Doods et al. (*J. Pharmacol. Exp. Ther.*, 242, 257-262, 1987) with some modifications. The cardiac membrane sample, [³H]-quinuclidinyl benzilate and the test compound were incubated in a 0.5 ml HEPES buffer at 25°C for 45 minutes, followed by suction filtration through a glass filter (Whatman GF/B). The filter was washed three times with 5 ml portions of an HEPES buffer. The radioactivity of the [³H]-quinuclidinyl benzilate adsorbed on the filter was measured by a liquid scintillation counter. Incidentally,

non-specific binding of the receptor was determined by the addition of 1 μ M atropine. The ^{binding}~~affinity~~ of the compound of the present invention for the muscarinic M_2 receptor was determined from a dissociation constant (K_i) calculated, in accordance with Chen and Prusoff (*Biochem. Pharmacol.* 22, 3099, 1973), based on the concentration (IC_{50}) of the test compound at which 50% of the binding of the [3H]-quinuclidinyl benzilate, that is, a labeled ligand was inhibited.

c. Muscarinic M_3 receptor binding test

In a similar manner to the above muscarinic M_2 receptor binding test except that the submandibular gland was used as a membrane sample and [3H]-N-methylscopolamine was used as a labeled ligand, a muscarinic M_3 receptor binding test was carried out.

Results: The compound (I) of the present invention had a K_i value of from 10^{-8} to 10^{-10} for M_3 receptor, which suggested that the affinity for M_3 receptor was at least 10 times as high as that for M_2 receptor.

Muscarinic receptor antagonism test (*in vivo*)

a. Test on rhythmic bladder contraction in rat

A female Wistar rat (130-200 g) was subjected to urethane anesthesia (1.0 g/kg s.c.), followed by ligation of the ureter on the kidney side. A urethral catheter was allowed to remain in the bladder, and about 1.0 ml of physiological saline was injected into the bladder through

the catheter to cause rhythmic bladder contraction.

Intravesical pressure was measured by a pressure transducer.

After rhythmic contraction continued stable for at least 5 minutes, the test compound was cumulatively administered from the external jugular vein. Five to ten minutes later, the intravesical pressure was measured. An inhibition ratio of bladder contraction was determined compared with the bladder contraction before administration of the test compound and the dose of the test compound required for 30% inhibition of the bladder contraction before administration was designated as ED₃₀.

As a result of the test, the compound of the present invention showed good ED₃₀ value.

b. Test on salivary secretion in rat

A male Wistar rat (160-190 g) was subjected to anesthesia with urethane (0.8 g/kg i.p.), and the test compound was administered (to the control group: solvent). Fifteen minutes later, 0.8 μmol/kg of oxotremorine was administered. In each case, the drug was administered through its femoral artery. The saliva secreted for 5 minutes after the administration of oxotremorine was collected and weighed. The inhibition ratio against the amount of saliva in the control group was determined and the dose of the test compound required for 50% inhibition of the amount of saliva in the control group was designated as ID₅₀.

As a result of the test, the ID₅₀ value of atropine tested as a comparative compound was substantially the same with the ED₃₀ value obtained in the above rat rhythmical bladder contraction test, while the ID₅₀ value of the invention compound was at least 5 times as much as the above-described ED₃₀ value, which suggested that the compound of the present invention has relatively weak action against the salivary secretion.

c. Test on bradycardia in rat

The test was carried out in accordance with the method of Doods et al. (*J. Pharmacol. Exp. Ther.*, 242, 257-262, 1987). A male Wistar rat (250-350 g) was subjected to anesthesia with pentobarbital sodium (50 mg/kg i.p.). The neck region was excised, followed by the division of right and left vagus nerves. After a cannula was inserted into a trachea to secure airway, a stainless rod was inserted from the orbit and the spinal cord was destroyed. Under artificial respiration (at 10 cc/kg and 50 times/minute), the rectal temperature was maintained at 37.5°C and a heart rate was monitored at the common carotid artery. An indwelling needle was fixed to the femoral artery, from which the drug was administered. After the destruction of the spinal cord, the rat was allowed to stand for 15 minutes to attain the equilibrium, followed by the administration of atenolol (10 mg/kg). After the equilibration for additional 15 minutes, the test compound was administered. Fifteen minutes

later, oxotremorine was cumulatively administered, thereby the reduction in the heart rate was measured. The amount of the test compound required for 10-times rightward shift of the dose-response curve of the control group was designated as DR₁₀.

Results: The compound (I) of the present invention had sufficiently low activity against bradycardia and no bradycardia was observed at the administration amount of several mg/kg.

As a result of the above-described muscarinic receptor ^{binding}~~affinity~~ test (*in vitro*), it was found that the compound (I) of the present invention had selectivity and high affinity for M₃ receptor. Even in the muscarinic receptor antagonism test (*in vivo*), the compound of the present invention showed good muscarinic M₃ antagonistic activity but low activity on the bradycardia having relationship with muscarinic M₂ receptor. Accordingly, it was found that the compound (I) of the present invention has selective antagonistic activity against muscarinic M₃ receptor, and furthermore, it has less side effects such as dry mouth compared with the conventional anti-cholinergic agent.

A pharmaceutical composition containing one or more of the compounds of the present invention and salts thereof is prepared using an ordinary pharmaceutically acceptable carrier.

In the present invention, the administration of the pharmaceutical composition can be carried out either orally or parenterally in the form of an injection, suppository, transdermal agent, inhalant or intravesical injection.

5 The dose is optionally determined in each case in consideration of the conditions, age, sex and the like of the patient to be administered. In the oral administration, the daily dose may generally range from about 0.01 mg/kg to 100 mg/kg per adult. It is administered once or in 2-4 portions. Where intravenous administration is adopted in consideration of the conditions of the patient, the daily dose may generally range from about 0.001 mg/kg to 10 mg/kg per adult, once or plural portions per day.

10 Examples of the pharmaceutical carrier include nontoxic solid or liquid pharmaceutical substances.

15 Examples of the solid composition for the oral administration include tablets, pills, capsules, powders and granules, or the like. In such solid compositions, one or more active substances are mixed with at least one inert diluent such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, agar, pectin, magnesium metasilicate or magnesium aluminate. In the composition, it is possible to incorporate additives other than the above inert diluent, for
20 example, a lubricant such as magnesium stearate, a disintegrator such as cellulose calcium glycolate, a
25

stabilizer such as lactose, a solubilization aid such as glutamic acid or aspartic acid in a conventional manner. A tablet or pill may optionally be coated with sugar or a film of a gastric or enteric substance such as sucrose, gelatin, hydroxypropylcellulose or hydroxypropylmethylcellulose phthalate.

Examples of the liquid composition for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs which contain a commonly employed inert diluent such as purified water or ethanol. The composition can also contain, in addition to such an inert diluent, a wetting agent, auxiliary agent such as suspending agent, sweetener, flavoring agent, aroma and/or antiseptic.

The injection for parenteral administration according to the present invention include a sterile aqueous or nonaqueous solution, suspension or emulsion. Examples of the aqueous solution and suspension include distilled water and physiological saline for injection. Examples of the non-water-soluble solution or suspension include ethylene glycol, polypropylene glycol, polyethylene glycol, vegetable oils such as cacao butter, olive oil or sesame oil, alcohols such as ethanol, gum arabic and "Polysolvate 80" (trade name). Such a composition may further contain an isotonicity agent, antiseptic agent, wetting agent, emulsifying agent, dispersing agent, stabilizer (for example, lactose) and/or

solubilizing aid (for example, glutamic acid, aspartic acid). They are sterilized by, for example, filtration through a bacteria-retaining filter, incorporation of a sterilizer, or irradiation. Alternatively, a sterile solid composition which has been prepared in advance is dissolved in sterile water or a sterile injection solvent upon use.

Best Modes for Carrying out the Invention

The present invention will hereinafter be described in further detail with reference to the following Examples. However, the compounds of the present invention should not be construed as being limited to the compounds which will be described later in Examples but embrace all the compounds represented by the above formula (I) and salts, hydrates, solvates, geometrical and optical isomers and any polymorphism forms of the compound (I).

Incidentally, the starting compounds for the compound of the present invention include novel compounds and preparation examples of such starting compounds will be described below as Reference Examples.

Reference Example 1

To a 130 ml dichloromethane solution containing 6.28 g of 1-phenyl-1,2,3,4-tetrahydroisoquinoline and 3.34 g of triethylamine, 3.1 ml of ethyl chloroformate was added dropwise under ice-cooling, followed by stirring at room temperature overnight. The reaction solution was washed

successively with water, 1N hydrochloric acid, water and brine and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, thereby 10.58 g of ethyl 1-phenyl-1,2,3,4-tetrahydro-2-

5 isoquinolinecarboxylate was obtained as pale yellow oil. Infrared absorption spectrum $\nu_{\max}(\text{neat})\text{cm}^{-1}$: 1700, 1430, 1296, 1230, 1122.

Nuclear magnetic resonance spectrum (CDCl_3 , TMS internal standard)

10 δ : 1.29 (3H, t, $J = 7.3$ Hz), 2.75-3.45 (3H, m), 3.90-4.40 (1H, m), 4.21 (2H, q, $J = 7.3$ Hz), 6.38 (1H, s), 6.95-7.45 (9H, m).

In a similar manner to Reference Example 1, the compounds of the following Reference Examples 2 to 14 were
15 obtained.

Reference Example 2

Methyl 1-phenyl-2-isoindolinecarboxylate

Starting compounds: 1-phenylisoindoline, methyl chloroformate

20 Infrared absorption spectrum $\nu_{\max}(\text{KBr})\text{cm}^{-1}$: 1708, 1460, 1376, 1100

Nuclear magnetic resonance spectrum (CDCl_3 , TMS internal standard)

25 δ : 3.60, 3.72 (3H, s \times 2), 4.89, 4.96 (2H, s \times 2), 5.94, 6.03 (1H, s \times 2), 6.95-7.10 (1H, m), 7.15-7.35 (8H, m)

Reference Example 3

Ethyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate

Starting compound: 1-(4-pyridyl)-1,2,3,4-
tetrahydroisoquinoline

Properties: pale yellow oil

Mass analysis (m/z, EI): 282 (M^+)

Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal
standard)

δ : 1.29 (3H, t, $J = 7.1$ Hz), 2.60-3.45 (3H, m), 3.85-
4.20 (1H, m), 4.22 (2H, q, $J = 7.1$ Hz), 6.31 (1H, s),
7.14 (2H, dd, $J = 4.4, 1.5$ Hz), 7.17-7.26 (4H, m),
8.51 (2H, dd, $J = 4.4, 1.5$ Hz)

Reference Example 4

Ethyl 1,2,3,4-tetrahydro-1-(2-thienyl)-2-
isoquinolinecarboxylate

Starting compound: 1,2,3,4-tetrahydro-1-(2-
thienyl)isoquinoline

Properties: pale yellow oil

Mass analysis (m/z, EI): 287 (M^+)

Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal
standard)

δ : 1.32 (3H, t, $J = 7.3$ Hz), 2.65-3.60 (3H, m), 4.00-
4.30 (1H, m), 4.23 (2H, q, $J = 7.3$ Hz), 6.53 (1H, s),
6.70-6.95 (2H, m), 7.15-7.30 (5H, m)

Reference Example 5

Ethyl 1,2,3,4-tetrahydro-1-(3-thienyl)-2-
isoquinolinecarboxylate

Starting compound: 1,2,3,4-tetrahydro-1-(3-thienyl)-
isoquinoline

Properties: Orange oil

Mass analysis (m/z, FAB): 288 $-(M^+ + 1)$

Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal
standard)

δ : 1.2-1.3 (3H, m), 2.7-2.8 (1H, m), 2.9-3.0 (1H, m),
3.1-3.3 (1H, m), 3.9-4.2 (3H, m), 6.2-6.4 (1H, m),
6.83 (1H, s), 6.95-7.26 (6H, m)

Reference Example 6

Ethyl 1-(2-furyl)-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate

Starting compound: 1-(2-furyl)-1,2,3,4-
tetrahydroisoquinoline

Mass analysis (m/z, EI): 271 (M^+)

Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal
standard)

δ : 1.30 (3H, t, $J = 6.5$ Hz), 2.75-2.85 (1H, m), 2.90-
3.10 (1H, m), 3.20-3.50 (1H, m), 4.05-4.35 (4H, m),
6.00 (1H, s), 6.20-6.45 (2H, m), 7.15-7.25 (4H, m),
7.33 (1H, s)

34

Reference Example 7

(1~~R~~)-Ethyl 1-phenyl-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate

Starting compound: (1~~R~~)₅-1-phenyl-1,2,3,4-
tetrahydroisoquinoline

Elemental analysis (for C₁₈H₁₉NO₂)

| | C (%) | H (%) | N (%) |
|---------|-------|-------|-------|
| Calcd.: | 76.84 | 6.81 | 4.98 |
| Found: | 76.53 | 6.82 | 4.93 |

Specific optical rotation $[\alpha]_D^{25}$: 199.2 ($c = 1.03$, CHCl₃)

Mass analysis (m/z, FAB): 282 (M⁺ + 1)

Reference Example 8

(1~~R~~)₂-Ethyl 1-phenyl-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate

Starting compound: (1~~R~~)₅-1-phenyl-1,2,3,4-
tetrahydroisoquinoline

Elemental analysis (for C₁₈H₁₉NO₂)

| | C (%) | H (%) | N (%) |
|---------|-------|-------|-------|
| Calcd.: | 76.84 | 6.81 | 4.98 |
| Found: | 76.64 | 6.82 | 4.99 |

Specific optical rotation $[\alpha]_D^{25}$: -200.9 ($c = 1.09$, CHCl₃)

Mass analysis (m/z, EI): 281 (M⁺)

Reference Example 9

Ethyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate

Starting compound: 1-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline

Properties: Pale yellow oil

Mass analysis (m/z, EI): 315 (M^+)

5 Nuclear magnetic resonance spectrum ($CDCl_3$, TMS Internal standard)

δ : 1.29 (3H, t, $J = 7.0$ Hz), 2.70-3.52 (3H, m), 4.00-4.30 (1H, m), 4.20 (2H, q, $J = 7.0$ Hz), 6.35 (1H, s), 7.05-7.35 (8H, m)

10 Reference Example 10

Ethyl 1-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline

15 Properties: Pale yellow oil

Mass analysis (m/z, FAB): 300 ($M^+ + 1$)

Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard)

20 δ : 1.30 (3H, t, $J = 8.9$ Hz), 2.75 (1H, dd, $J = 12.5, 3.4$ Hz), 2.9-3.1 (1H, m), 3.1-3.3 (1H, m), 4.0-4.3 (3H, m), 6.2-6.4 (1H, m), 6.93-7.03 (3H, m), 7.16-7.24 (5H, m).

Reference Example 11

25 Ethyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-isoquinolinecarboxylate

Starting compound: 1,2,3,4-tetrahydro-1-(4-tolyl)isoquinoline

Mass analysis (m/z, EI): 295 (M^+)

Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard)

δ : 1.20-1.35 (3H, m), 2.30 (3H, s), 2.70-2.80 (1H, m),
2.90-3.10 (1H, m), 3.23 (1H, t, $J = 10.0$ Hz),
3.95-4.30 (3H, m), 6.29, 6.41 (1H, brs $\times 2$),
7.00-7.25 (8H, m).

Reference Example 12

Ethyl 1-benzyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-benzyl-1,2,3,4-tetrahydroisoquinoline

Properties: Pale yellow oil

Mass analysis (m/z, FAB): 296 ($M^+ + 1$)

Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard)

δ : 1.02, 1.23 (3H, t $\times 2$, $J = 7.1$ Hz), 2.63-3.20
(4H, m), 3.30-3.50 (1H, m), 3.75-4.25 (3H, m), 5.27,
5.38 (1H, t $\times 2$, $J = 6.8$ Hz), 6.85-7.28 (9H, m).

Reference Example 13

Ethyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: 1-cyclohexyl-1,2,3,4-tetrahydroisoquinoline

Properties: yellow oil

Mass analysis (m/z, FAB): 288 ($M^+ + 1$)

Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard)

5 δ : 0.70-2.00 (11H, m), 1.26 (3H, t, $J = 7.3$ Hz),
2.89 (2H, t, $J = 7.1$ Hz), 3.25-4.20 (2H, m), 4.14
(2H, q, $J = 7.1$ Hz), 4.65-4.95 (1H, m), 7.00-7.30
(4H, m).

Reference Example 14

Ethyl 1-(3-furyl)-1,2,3,4-tetrahydro-2-
10 isoquinolinecarboxylate

Starting compound: 1-(3-furyl)-1,2,3,4-
tetrahydroisoquinoline

Properties: yellow oil

Mass analysis (m/z, EI): 271 (M^+)

15 Nuclear magnetic resonance spectrum ($CDCl_3$, TMS internal standard)

δ : 1.31 (3H, t, $J = 7.0$ Hz), 2.55-3.40 (3H, m), 3.90-
4.30 (1H, m), 4.22 (2H, q, $J = 7.0$ Hz), 6.20-6.45
(2H, m), 6.95-7.40 (6H, m).

20 The chemical structural formulas of the compounds
obtained in Reference Examples 1-14 are shown in the
following Tables 1-2.

T390X

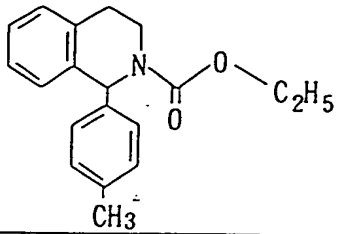
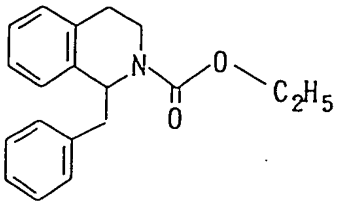
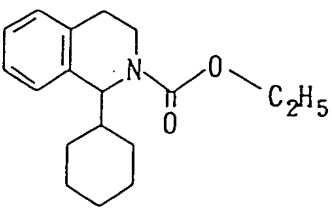
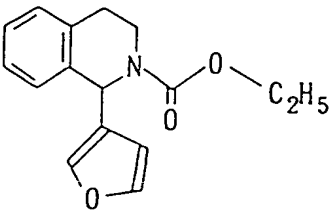
Table 1

| Reference Example No. | Structural Formula | Reference Example No. | Structural Formula |
|-----------------------|--------------------|-----------------------|--------------------|
| 1 | | 6 | |
| 2 | | 7 | |
| 3 | | 8 | |
| 4 | | 9 | |
| 5 | | 10 | |

T400X

08860377 082897
 168280 1609880

Table 2

| Reference Example No. | Structural Formula |
|-----------------------------|--|
| 11 |  |
| 12 |  |
| 13 |  |
| 14 |  |

Example 1

To a 30 ml toluene solution containing 0.70 g of ethyl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate and 0.41 g of 3-quinuclidinol, 0.03 g of sodium hydride (60%) was added. The resulting mixture was stirred at 140°C for 2 days while removing the ethanol formed. The reaction mixture was cooled to room temperature, brine was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform : methanol = 10 : 1 → chloroform : methanol : 28% aqueous ammonia = 10 : 1 : 0.1), thereby 0.11 g of 3-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was obtained as yellow oil. The resulting oil was dissolved in 10 ml of ethanol, followed by the addition of 27 mg of oxalic acid. Then, the solvent was removed under reduced pressure. The resulting solid was recrystallized from isopropanol and isopropyl ether, thereby 0.08 g of 3-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monooxalate was obtained as colorless crystals.

Melting point: 122-124°C (i-PrOH-i-Pr₂O)

41

Elemental analysis (for $C_{25}H_{28}N_2O_6 \cdot 0.75H_2O$)

| | C (%) | H (%) | N (%) |
|---------|-------|-------|-------|
| Calcd.: | 64.43 | 6.38 | 6.01 |
| Found: | 64.25 | 6.15 | 5.88 |

In a similar manner to Example 1, the compound of Example 2 was obtained.

Example 2

3-Quinuclidinyl 1-phenyl-2-isoindolinecarboxylate monohydrochloride

Starting compound: methyl 1-phenyl-2-isoindolinecarboxylate

Melting point: $164-165^{\circ}C$ (EtOH-Et₂O)

Elemental analysis (for $C_{22}H_{25}N_2O_2Cl \cdot 1.75H_2O$)

| | C (%) | H (%) | N (%) | Cl (%) |
|---------|-------|-------|-------|--------|
| Calcd.: | 63.45 | 6.90 | 6.73 | 8.51 |
| Found: | 63.54 | 6.59 | 6.76 | 8.12 |

Example 3

To a 50 ml toluene suspension containing 720 mg of ethyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate and 973 mg of 3-quinuclidinol, 102 mg of sodium hydride (60%) was added at room temperature. The resulting mixture was heated under reflux for 5 hours and 40 minutes while the resulting ethanol was removed together with toluene. The reaction mixture was cooled to room temperature, followed by addition of 20 ml of water. The resulting mixture was extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous

sodium sulfate and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (chloroform : methanol : 28% aqueous ammonia = 100 : 2 : 1), thereby 827 mg of 3-quinuclidinyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate were obtained as yellow oil. The resulting oil was dissolved in 5 ml of ethyl acetate, 2 ml of a 4N hydrogen chloride in ethyl acetate solution was added. The solvent was then removed under reduced pressure. Ethanol and ether were added to the residue, and the crude crystals thus obtained was recrystallized from ethanol and ether, thereby 402 mg of 3-quinuclidinyl 1-(4-pyridyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate dihydrochloride was obtained as pale yellow crystals.

Melting point: 167-169°C (EtOH-Et₂O)

Elemental analysis (for C₂₂H₂₇N₃O₂Cl₂•2.2H₂O)

| | C (%) | H (%) | N (%) | Cl (%) |
|---------|-------|-------|-------|--------|
| Calcd.: | 55.51 | 6.65 | 8.83 | 14.90 |
| Found: | 55.46 | 6.98 | 8.64 | 14.84 |

In a similar manner to Example 3, the compounds of Examples 4 to 6 which will be described below were obtained.

Example 4

3-Quinuclidinyl 1,2,3,4-tetrahydro-1-(2-thienyl)-2-isoquinolinecarboxylate monooxalate

Starting compound: Ethyl 1,2,3,4-tetrahydro-1-(2-thienyl)-2-isoquinolinecarboxylate

Elemental analysis (for $C_{23}H_{26}N_2O_6S \cdot 1.3H_2O$)

| | C (%) | H (%) | N (%) | S (%) |
|---------|-------|-------|-------|-------|
| Calcd.: | 57.32 | 5.98 | 5.81 | 6.65 |
| Found: | 57.62 | 6.00 | 5.84 | 6.27 |

Mass analysis (m/z, FAB): 369 ($M^+ + 1$)

Example 5

(1RS,3'R)-3'-Quinuclidinyl 1,2,3,4-tetrahydro-1-(3-thienyl)-2-isoquinolinecarboxylate

Starting compounds: ethyl 1,2,3,4-tetrahydro-1-(3-thienyl)-2-isoquinolinecarboxylate, (3R)-3-quinuclidinol

Properties: Brown oil

Elemental analysis (for $C_{21}H_{24}N_2O_2S \cdot 0.3H_2O$)

| | C (%) | H (%) | N (%) | S (%) |
|---------|-------|-------|-------|-------|
| Calcd.: | 67.46 | 6.63 | 7.49 | 8.58 |
| Found: | 67.35 | 6.76 | 7.21 | 8.46 |

Mass analysis (m/z, FAB): 369 ($M^+ + 1$)

Example 6

3-Quinuclidinyl 1-(2-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: ethyl 1-(2-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Properties: Pale yellow oil

Elemental analysis (for $C_{21}H_{24}N_2O_3 \cdot 0.5H_2O$)

| | C (%) | H (%) | N (%) |
|---------|-------|-------|-------|
| Calcd.: | 69.79 | 6.97 | 7.75 |
| Found: | 70.03 | 7.05 | 7.44 |

Mass analysis (m/z, FAB): 353 ($M^+ + 1$)

Example 7

To a 30 ml pyridine solution containing 2.09 g of (1R)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, 2.26 g of 3-quinuclidinyl chloroformate monohydrochloride was added at room temperature, followed by stirring at 80°C for 4 hours. Then, 0.12 g of 3-quinuclidinyl chloroformate monohydrochloride, followed by stirring at 80°C for 4 hours. Then, 1.01 g of 3-quinuclidinyl chloroformate monohydrochloride was added, and the mixture was stirring at 80°C for 25 hours. The reaction mixture was concentrated under reduced pressure. Water was added to the residue, followed by washing with ethyl acetate twice. The resulting aqueous layer was adjusted to pH 9 with saturated sodium hydrogencarbonate aqueous solution, followed by extraction with ethyl acetate. After the organic layer was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, thereby 3.02 g of (1R,3'RS)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate was obtained as yellow oil.

Mass analysis (m/z, FAB): 363 ($M^+ + 1$)

Nuclear magnetic resonance spectrum (DMSO-d₆, TMS internal standard)

8: 1.20-2.00 (5H, m), 2.40-2.95 (6H, m), 3.00-3.60 (3H, m), 3.80-3.95 (1H, m), 4.55-4.70 (1H, m), 6.25 (1H, brs), 7.05-7.35 (10H, m).

Example 8

To a 120 ml toluene suspension containing 12.0 g of (1^SR)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate and 16.27 g of (3R)-3-quinuclidinol, 1.69 g of sodium hydride (60%) was added at room temperature. The resulting mixture was heated for 3 hours while the resulting ethanol was removed together with toluene. The reaction mixture was cooled to room temperature, and 50 ml of brine was added, followed by extraction with ethyl acetate. The organic layer was washed with water and then extracted with 20% hydrochloric acid. The resulting aqueous layer was adjusted to pH 9 to 10 by adding a 1N aqueous solution of sodium hydroxide, followed by extraction with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was dissolved in 140 ml of ethanol, and 10 ml of a 4N hydrogen chloride in ethyl acetate solution was added to the resulting solution. The solvent was then removed under reduced pressure. Acetonitrile and ether were added to the residue, and the resulting crude crystals were recrystallized from acetonitrile and ether, thereby 10.1 g of (1^SR,3'R)-3'-

quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate monohydrochloride was obtained as
colorless crystals.

Melting point: 212-214°C (CH₃CN-Et₂O)

Elemental analysis (for C₂₃H₂₇N₂O₂Cl)

| | C (%) | H (%) | N (%) | Cl (%) |
|---------|-------|-------|-------|--------|
| Calcd.: | 69.25 | 6.82 | 7.02 | 8.89 |
| Found: | 69.24 | 6.89 | 7.03 | 8.97 |

Specific optical rotation $[\alpha]_D^{25}$: 98.1 (C = 1.00, EtOH)

In a similar manner to Example 8, the compounds of
the following Examples 9 to 16 were obtained.

Example 9

(1^S,3'^S)-3'-quinuclidinyl 1-phenyl-1,2,3,4-
tetrahydro-2-isoquinolinecarboxylate monohydrochloride

Starting compounds: (1^S)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate, (3S)-3-quinuclidinol

Melting point: 211-212°C (EtOH-Et₂O)

Elemental analysis (for C₂₃H₂₇N₂O₂Cl•0.25H₂O)

| | C (%) | H (%) | N (%) | Cl (%) |
|---------|-------|-------|-------|--------|
| Calcd.: | 68.48 | 6.87 | 6.94 | 8.79 |
| Found: | 68.32 | 6.75 | 6.94 | 8.94 |

Specific optical rotation $[\alpha]_D^{25}$: -97.4 (C = 0.50, EtOH)

Example 10

(1^S,3'^R)-3'-quinuclidinyl 1-phenyl-1,2,3,4-
tetrahydro-2-isoquinolinecarboxylate monohydrochloride

Starting compounds: (^R1~~S~~)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (3R)-3-quinuclidinol

Melting point: 195-196°C (EtOH-Et₂O)

Elemental analysis (for C₂₃H₂₇N₂O₂Cl•0.25H₂O)

| | C (%) | H (%) | N (%) | Cl (%) |
|---------|-------|-------|-------|--------|
| Calcd.: | 68.48 | 6.87 | 6.94 | 8.79 |
| Found: | 68.73 | 6.88 | 6.95 | 8.70 |

Specific optical rotation [α]_D²⁵: -151.2 (C = 0.50, EtOH)

Example 11

(^S1~~R~~, 3'S)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monohydrochloride

Starting compounds: (^S1~~R~~)-ethyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (3S)-3-quinuclidinol

Melting point: 194-195°C (CH₃CN-Et₂O)

Elemental analysis (for C₂₃H₂₇N₂O₂Cl)

| | C (%) | H (%) | N (%) | Cl (%) |
|---------|-------|-------|-------|--------|
| Calcd.: | 69.25 | 6.82 | 7.02 | 8.89 |
| Found: | 69.08 | 6.71 | 6.99 | 8.91 |

Specific optical rotation [α]_D²⁵: 163.2 (C = 0.50, EtOH)

Example 12

3-quinuclidinyl 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate monofumarate

Starting compounds: 1-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Melting point: 164-166°C (EtOH-Et₂O)

Elemental analysis (for $C_{27}H_{29}N_2O_6Cl \cdot 0.5H_2O$)

| | C (%) | H (%) | N (%) | Cl (%) |
|---------|-------|-------|-------|--------|
| Calcd.: | 62.13 | 5.79 | 5.37 | 6.79 |
| Found: | 62.19 | 5.68 | 5.23 | 6.49 |

Example 13

(1RS,3'R)-3'-quinuclidinyl 1-(4-fluorophenyl)-
1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compounds: ethyl 1-(4-fluorophenyl)-1,2,3,4-
tetrahydro-2-isoquinolinecarboxylate, (3R)-3-quinuclidinol

Properties: colorless oil

Elemental analysis (for $C_{23}H_{25}N_2O_2F \cdot 0.1H_2O$)

| | C (%) | H (%) | N (%) | F (%) |
|---------|-------|-------|-------|-------|
| Calcd.: | 72.27 | 6.64 | 7.33 | 4.97 |
| Found: | 72.05 | 6.63 | 7.15 | 4.99 |

Mass analysis (m/z, FAB): 381 ($M^+ + 1$)

Example 14

3-quinuclidinyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-
isoquinolinecarboxylate

Starting compounds: ethyl 1,2,3,4-tetrahydro-1-(4-tolyl)-2-
isoquinolinecarboxylate

Properties: colorless oil

Elemental analysis (for $C_{24}H_{28}N_2O_2 \cdot 0.8H_2O$)

| | C (%) | H (%) | N (%) |
|---------|-------|-------|-------|
| Calcd.: | 73.74 | 7.63 | 7.17 |
| Found: | 73.96 | 7.50 | 6.95 |

Mass analysis (m/z, FAB): 377 ($M^+ + 1$)

Example 15

3-Quinuclidinyl 1-benzyl-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate

Starting compound: ethyl 1-benzyl-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate

Properties: pale yellow oil

Elemental analysis (for $C_{24}H_{28}N_2O_2 \cdot 0.5H_2O$)

| | C (%) | H (%) | N (%) |
|---------|-------|-------|-------|
| Calcd.: | 74.78 | 7.58 | 7.26 |
| Found: | 74.95 | 7.83 | 7.18 |

Mass analysis (m/z, FAB): 377 ($M^+ + 1$)

Example 16

3-Quinuclidinyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate

Starting compounds: ethyl 1-cyclohexyl-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate

Properties: pale yellow amorphous

Elemental analysis (for $C_{23}H_{32}N_2O_2 \cdot 0.3H_2O$)

| | C (%) | H (%) | N (%) |
|---------|-------|-------|-------|
| Calcd.: | 73.88 | 8.79 | 7.49 |
| Found: | 73.76 | 8.75 | 7.37 |

Mass analysis (m/z, FAB): 369 ($M^+ + 1$)

Example 17

In 12 ml of dichloromethane, 1.20 g of (1R,3'R)-3'-
quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-
isoquinolinecarboxylate was dissolved, 0.33 g of sodium

hydrogencarbonate and 0.79 g of m-chloroperbenzoic acid (80%) were added under ice-cooling, followed by stirring at room temperature for one hour. Water was added to the reaction mixture and then the mixture was extracted with

5 dichloromethane. The organic layer was washed with an aqueous solution of sodium thiosulfate and then dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure, and the residue was purified by silica gel column chromatography (chloroform : methanol = 20:1), thereby 0.43 g of (1⁵R,3R)-3-[[(1'-phenyl-1',2',3',4'-tetrahydro-2'-isoquinolyl)carbonyl]oxy]quinuclidine 1-oxide was obtained.

Properties: white amorphous

Mass analysis (m/z, FAB): 379 (M⁺ + 1)

15 Nuclear magnetic resonance spectrum (CDCl₃, TMS internal standard)

20 δ: 1.85-2.15 (3H, m), 2.15-2.35 (2H, m), 2.75-2.90 (1H, m), 2.90-2.95 (1H, m), 3.20-3.50 (6H, m), 3.70-3.80 (1H, m), 3.85-4.10 (1H, m), 5.14 (1H, brs), 6.14, 6.43 (1H, brs x 2), 7.05-7.40 (9H, m).

Example 18

To a 8 ml 2-butanone solution containing 1.04 g of (1⁵R,3'R)-3'-quinuclidinyl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, 0.18 ml of methyl iodide was added,

25 followed by stirring at 55°C for 40 minutes. After air cooling, the crystals precipitated were collected by

filtration and then washed successively with 2-butanone and diethyl ether, thereby 0.93 g of (1'^S_R, 3R)-1-methyl-3-[[(1'-phenyl-1', 2', 3', 4'-tetrahydro-2'-isoquinolyl)carbonyl]oxy]quinuclidinium iodide was obtained as colorless crystals.

Melting point: 202-203°C (2-butanone)

Elemental analysis (for C₂₄H₂₉N₂O₂I)

| | C (%) | H (%) | N (%) | I (%) |
|---------|-------|-------|-------|-------|
| Calcd.: | 57.15 | 5.79 | 5.55 | 25.16 |
| Found: | 57.17 | 5.71 | 5.51 | 25.15 |

In a similar manner to Example 8, the compound of the following Example 19 was obtained.

Example 19

(1RS, 3'R)-3'-quinuclidinyl 1-(3-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Starting compound: ethyl 1-(3-furyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate

Properties: yellow oil

Elemental analysis (for C₂₁H₂₄N₂O₃•0.3H₂O)

| | C (%) | H (%) | N (%) |
|---------|-------|-------|-------|
| Calcd.: | 70.49 | 6.93 | 7.83 |
| Found: | 70.35 | 6.83 | 7.63 |

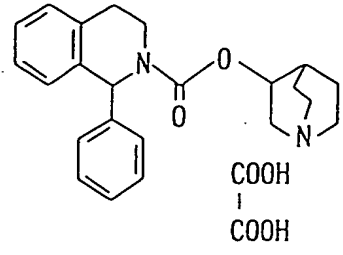
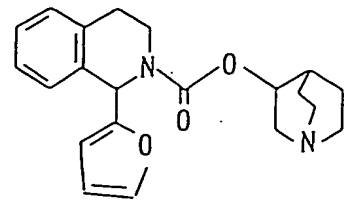
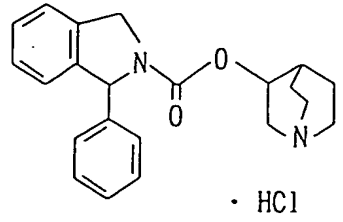
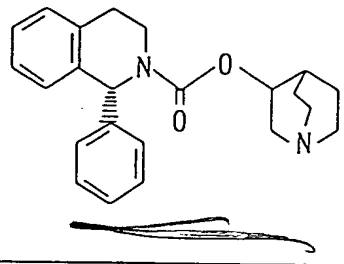
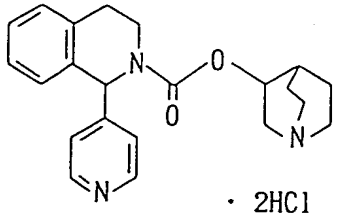
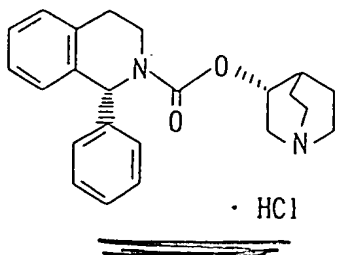
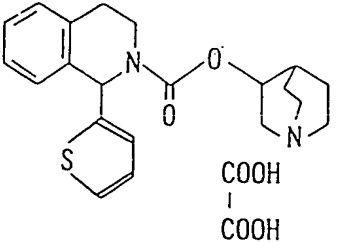
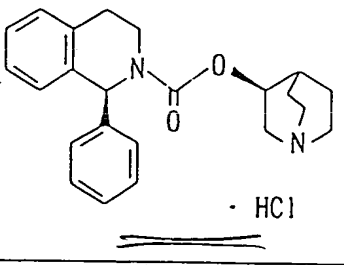
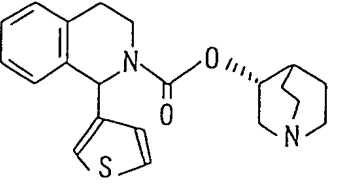
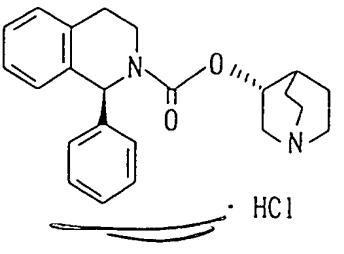
Mass analysis (m/z, EI): 352 (M⁺)

The chemical structural formulas of the compounds obtained in Examples 1-19 are shown below in Tables 3-5.

TS30X

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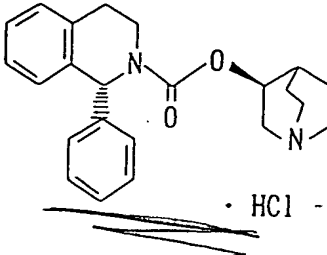
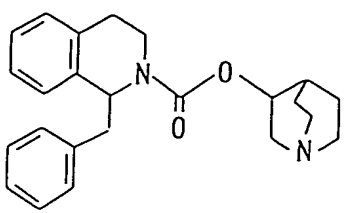
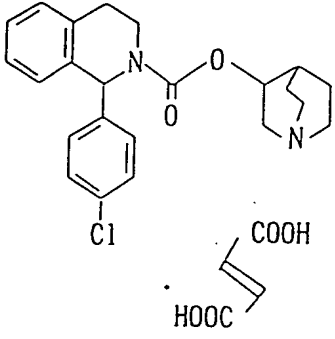
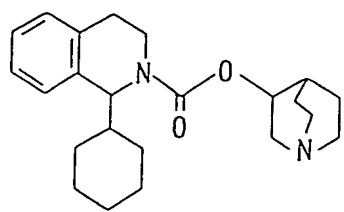
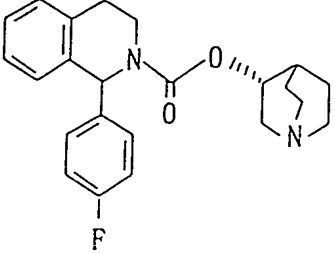
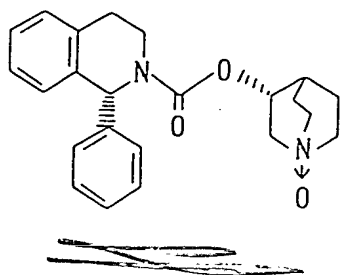
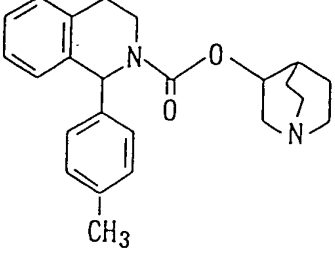
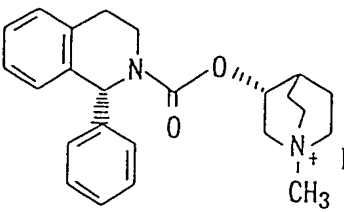
Table 3

| Example No. | Structural Formula | Example No. | Structural Formula |
|-------------|--|-------------|---|
| 1 |  | 6 |  |
| 2 |  • HCl | 7 |  |
| 3 |  • 2HCl | 8 |  • HCl |
| 4 |  COOH COOH | 9 |  • HCl |
| 5 |  | 10 |  • HCl |

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TS40X

Table 4

| Example No. | Structural Formula | Example No. | Structural Formula |
|-------------|---|-------------|--|
| 11 |  | 15 |  |
| 12 |  | 16 |  |
| 13 |  | 17 |  |
| 14 |  | 18 |  |

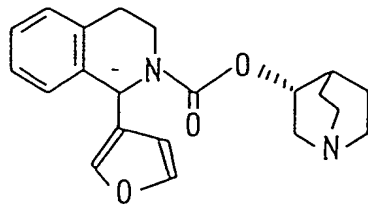
54

0886037 082897 268280 2609880

T550X

5

Table 5

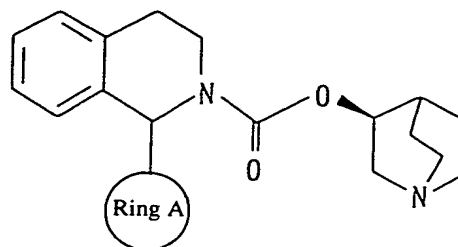
| Example No. | Structural Formula |
|-------------|--|
| 19 |  |

Each of the above-described compounds in Examples 3-6, 12-14, 16 and 19 can be obtained as an optical resolved form as shown in the following Tables 6-8 using an optically resolved intermediate in a similar manner to Examples 8-11.

55

TsOX

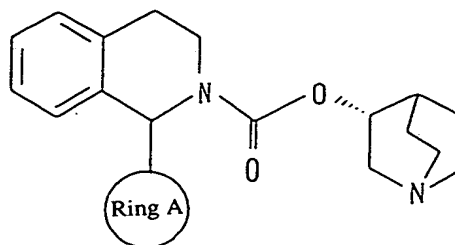
Table 6



| Example No. | Ring A | Example No. | Ring A |
|-------------|--------|-------------|--------|
| 3-(a) | | 3-(b) | |
| 4-(a) | | 4-(b) | |
| 5-(a) | | 5-(b) | |
| 6-(a) | | 6-(b) | |
| 12-(a) | | 12-(b) | |
| 13-(a) | | 13-(b) | |
| 14-(a) | | 14-(b) | |
| 16-(a) | | 16-(b) | |

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Table 7



| Example No. | Ring A | Example No. | Ring A |
|-------------|--------|-------------|--------|
| 3-(c) | | 3-(d) | |
| 4-(c) | | 4-(d) | |
| 5-(c) | | 5-(d) | |
| 6-(c) | | 6-(d) | |
| 12-(c) | | 12-(d) | |
| 13-(c) | | 13-(d) | |
| 14-(c) | | 14-(d) | |
| 16-(c) | | 16-(d) | |

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Table 8

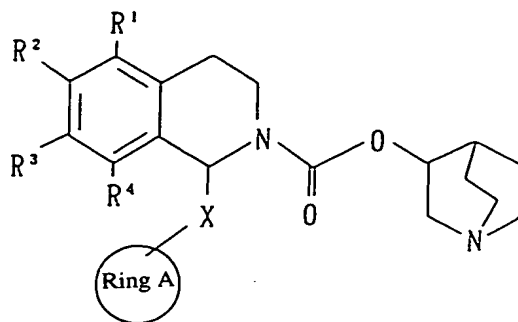
| Example No. | Structural Formula |
|-------------|--------------------|
| 19-(a) | |
| 19-(b) | |
| 19-(c) | |
| 19-(d) | |

The other compounds embraced by the present invention will be shown in Tables 9-33. They can be synthesized by any one of the above-described preparation processes, processes described in Examples or processes known to those skilled in the art and do not require any particular experiment.

Incidentally, these compounds are described as a racemic compound, but optical active substances based on an asymmetric carbon is also included.

T600X

Table 9

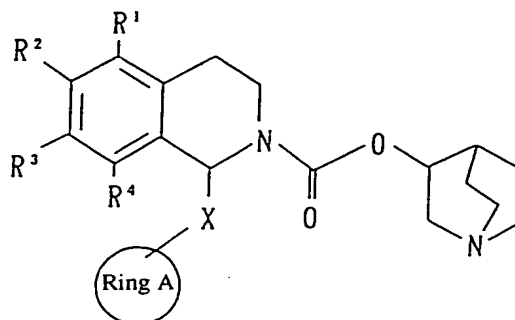


| Compound No. | R ¹ | R ² | R ³ | R ⁴ | X | Ring A |
|--------------|-----------------|----------------|----------------|----------------|---|--------|
| A - 1 | Cl | H | H | H | — | |
| A - 2 | H | H | Cl | H | — | |
| A - 3 | Cl | H | Cl | H | — | |
| A - 4 | F | H | H | H | — | |
| A - 5 | H | H | F | H | — | |
| A - 6 | Br | H | H | H | — | |
| A - 7 | H | H | Br | H | — | |
| A - 8 | Cl | H | Br | H | — | |
| A - 9 | CH ₃ | H | H | H | — | |

60

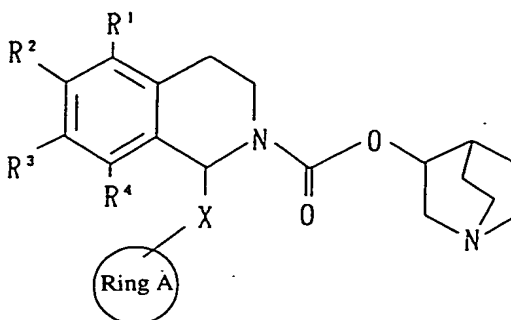
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Table 10



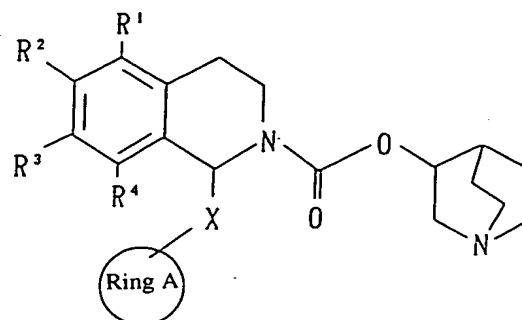
| Compound No. | R^1 | R^2 | R^3 | R^4 | X | Ring A |
|--------------|------------|----------|----------|-------|---|--------|
| A - 10 | C_2H_5 | H | H | H | — | |
| A - 11 | $n-C_3H_7$ | H | H | H | — | |
| A - 12 | $i-C_3H_7$ | H | H | H | — | |
| A - 13 | H | CH_3 | H | H | — | |
| A - 14 | H | C_2H_5 | H | H | — | |
| A - 15 | H | H | CH_3 | H | — | |
| A - 16 | H | H | C_2H_5 | H | — | |
| A - 17 | CH_3 | H | CH_3 | H | — | |
| A - 18 | H | CH_3 | CH_3 | H | — | |

Table 11



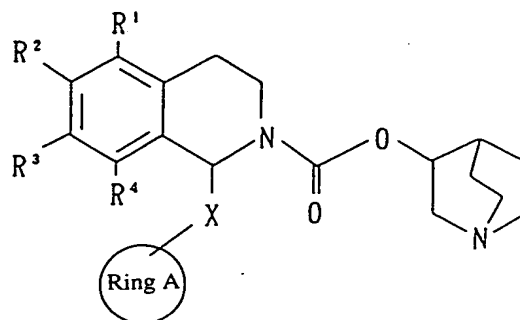
| Compound No. | R ¹ | R ² | R ³ | R ⁴ | X | Ring A |
|--------------|-----------------|----------------|-----------------|-----------------|---|--------|
| A - 19 | CH ₃ | H | CH ₃ | CH ₃ | — | |
| A - 20 | Cl | H | H | H | — | |
| A - 21 | H | H | Cl | H | — | |
| A - 22 | H | H | Cl | H | — | |
| A - 23 | H | H | Cl | H | — | |
| A - 24 | H | H | Cl | H | — | |
| A - 25 | H | H | Cl | H | — | |

Table 12



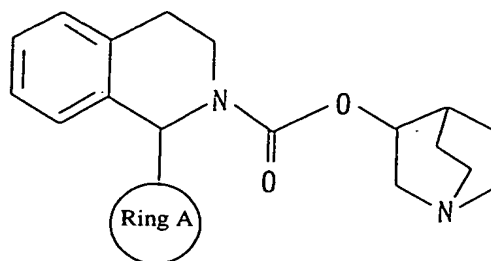
| Compound No. | R ¹ | R ² | R ³ | R ⁴ | X | Ring A |
|--------------|----------------|----------------------|------------------|----------------|---|--------|
| A - 26 | H | H | CH ₃ | H | — | |
| A - 27 | Cl | H | H | H | — | |
| A - 28 | H | CH ₃ | H | H | — | |
| A - 29 | Cl | H | H | H | — | |
| A - 30 | Cl | H | H | H | — | |
| A - 31 | H | H | Cl | H | — | |
| A - 32 | H | H | Cl | H | — | |
| A - 33 | H | OCH ₃ | OCH ₃ | H | — | |
| A - 34 | H | -OCH ₂ O- | | H | — | |

Table 13



| Compound No. | R ¹ | R ² | R ³ | R ⁴ | X | Ring A |
|--------------|----------------|----------------|----------------|----------------|-----------------|--------|
| A - 35 | H | H | H | H | CH ₂ | |
| A - 36 | H | H | H | H | CH ₂ | |
| A - 37 | H | H | H | H | CH ₂ | |
| A - 38 | H | H | H | H | CH ₂ | |
| A - 39 | H | H | H | H | CH ₂ | |
| A - 40 | Cl | H | H | H | CH ₂ | |
| A - 41 | Cl | H | H | H | CH ₂ | |
| A - 42 | Cl | H | H | H | CH ₂ | |

Table 14



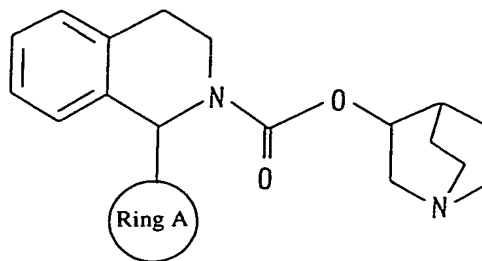
| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 1 | | B - 7 | |
| B - 2 | | B - 8 | |
| B - 3 | | B - 9 | |
| B - 4 | | B - 10 | |
| B - 5 | | B - 11 | |
| B - 6 | | B - 12 | |

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T660X

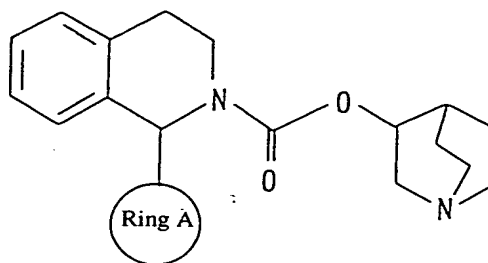
Table 15



| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 13 | | B - 19 | |
| B - 14 | | B - 20 | |
| B - 15 | | B - 21 | |
| B - 16 | | B - 22 | |
| B - 17 | | B - 23 | |
| B - 18 | | B - 24 | |

66p

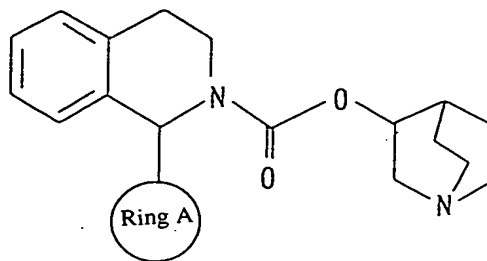
Table 16



| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 25 | | B - 31 | |
| B - 26 | | B - 32 | |
| B - 27 | | B - 33 | |
| B - 28 | | B - 34 | |
| B - 29 | | B - 35 | |
| B - 30 | | B - 36 | |

T680X

Table 17



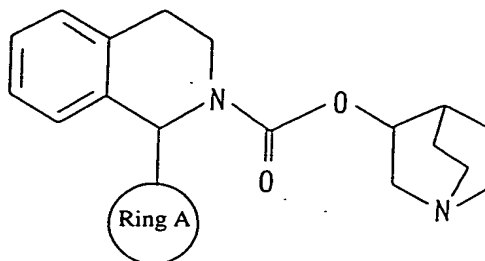
| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 37 | | B - 43 | |
| B - 38 | | B - 44 | |
| B - 39 | | B - 45 | |
| B - 40 | | B - 46 | |
| B - 41 | | B - 47 | |
| B - 42 | | B - 48 | |

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T690X

Table 18



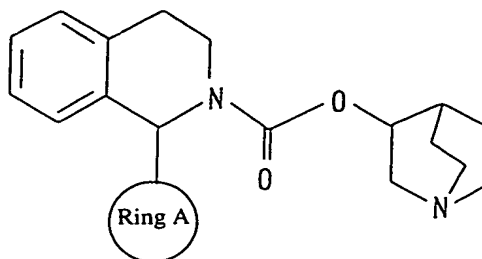
| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 49 | | B - 55 | |
| B - 50 | | B - 56 | |
| B - 51 | | B - 57 | |
| B - 52 | | B - 58 | |
| B - 53 | | B - 59 | |
| B - 54 | | B - 60 | |

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T700X

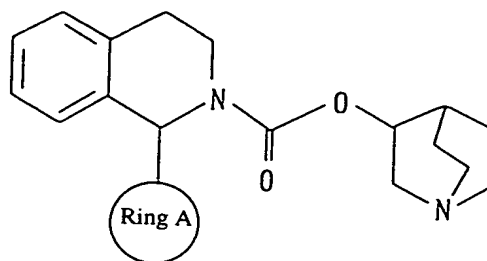
Table 19



| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 61 | | B - 67 | |
| B - 62 | | B - 68 | |
| B - 63 | | B - 69 | |
| B - 64 | | B - 70 | |
| B - 65 | | B - 71 | |
| B - 66 | | B - 72 | |

T110X

Table 20



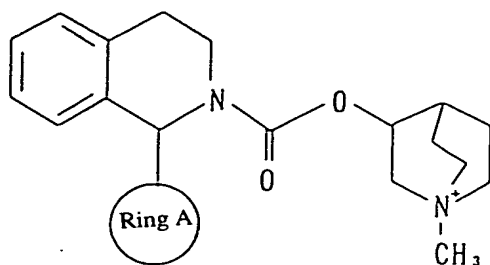
| Compound No. | Ring A |
|--------------|--------|
| B - 73 | |
| B - 74 | |
| B - 75 | |

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T120X

Table 21



X⁻

(X=Br, I)

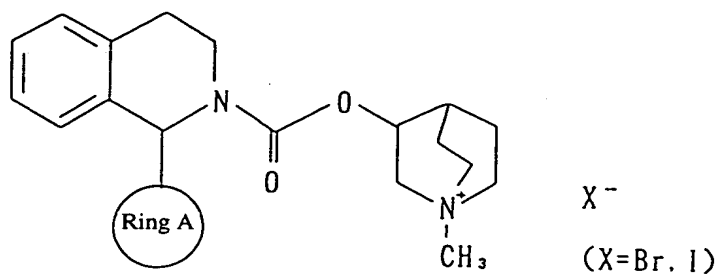
| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 76 | | B - 82 | |
| B - 77 | | B - 83 | |
| B - 78 | | B - 84 | |
| B - 79 | | B - 85 | |
| B - 80 | | B - 86 | |
| B - 81 | | B - 87 | |

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72

T130X

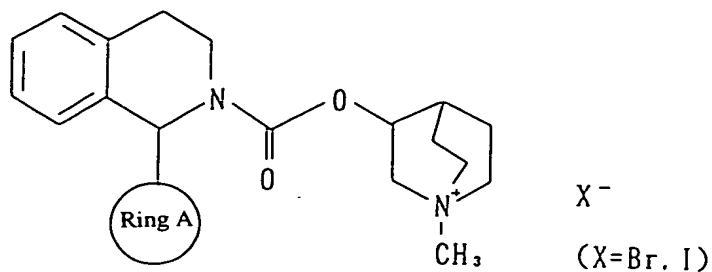
Table 22



| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 88 | | B - 94 | |
| B - 89 | | B - 95 | |
| B - 90 | | B - 96 | |
| B - 91 | | B - 97 | |
| B - 92 | | B - 98 | |
| B - 93 | | B - 99 | |

7740X

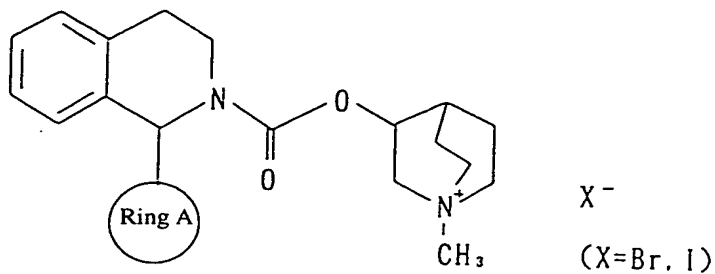
Table 23



| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 100 | | B - 106 | |
| B - 101 | | B - 107 | |
| B - 102 | | B - 108 | |
| B - 103 | | B - 109 | |
| B - 104 | | B - 110 | |
| B - 105 | | B - 111 | |

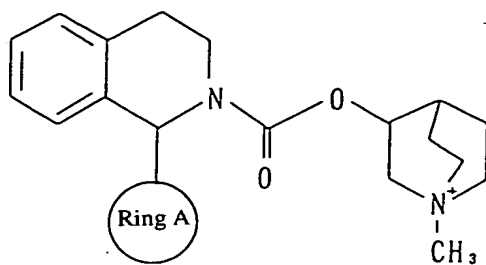
T7SOX

Table 24



| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 112 | | B - 118 | |
| B - 113 | | B - 119 | |
| B - 114 | | B - 120 | |
| B - 115 | | B - 121 | |
| B - 116 | | B - 122 | |
| B - 117 | | B - 123 | |

Table 25

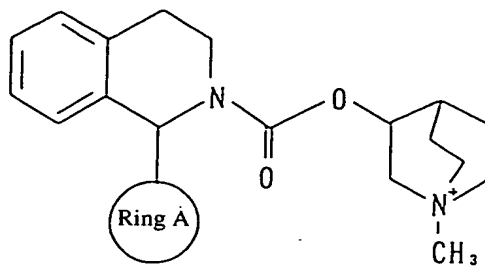


X^-
(X=Br, I)

| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 124 | | B - 130 | |
| B - 125 | | B - 131 | |
| B - 126 | | B - 132 | |
| B - 127 | | B - 133 | |
| B - 128 | | B - 134 | |
| B - 129 | | B - 135 | |

089037 082897 258280 2299880

Table 26



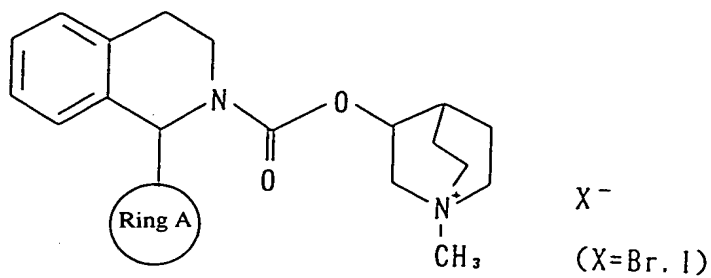
X⁻

(X=Br, I)

| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 136 | | B - 142 | |
| B - 137 | | B - 143 | |
| B - 138 | | B - 144 | |
| B - 139 | | B - 145 | |
| B - 140 | | B - 146 | |
| B - 141 | | B - 147 | |

T780X

Table 27



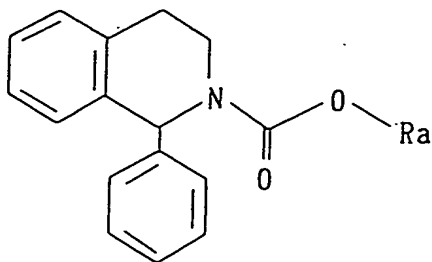
| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 148 | | B - 153 | |
| B - 149 | | B - 154 | |
| B - 150 | | B - 155 | |
| B - 151 | | B - 156 | |
| B - 152 | | | |

08360377-082897

78

T190x

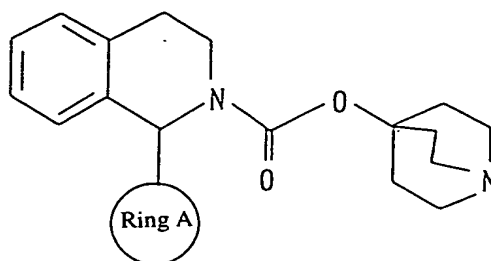
Table 28



| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 157 | | B - 158 | |

T800X

Table 29



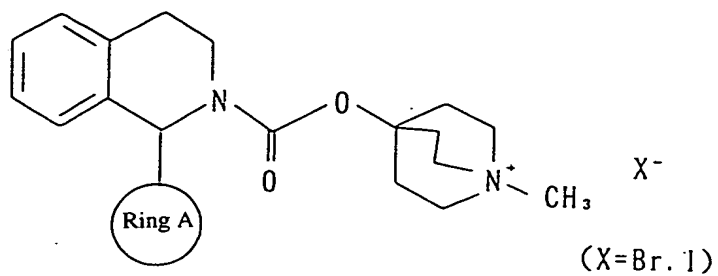
| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 159 | | B - 164 | |
| B - 160 | | B - 165 | |
| B - 161 | | B - 166 | |
| B - 162 | | B - 167 | |
| B - 163 | | B - 168 | |

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T810X

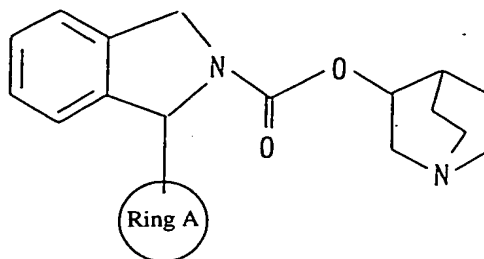
Table 30



| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 169 | | B - 174 | |
| B - 170 | | B - 175 | |
| B - 171 | | B - 176 | |
| B - 172 | | B - 177 | |
| B - 173 | | B - 178 | |

TR00X

Table 31

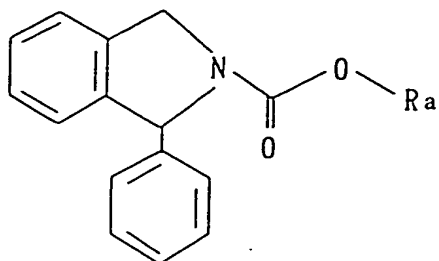


| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 179 | | B - 184 | |
| B - 180 | | B - 185 | |
| B - 181 | | B - 186 | |
| B - 182 | | B - 187 | |
| B - 183 | | | |

82

T830x

Table 32



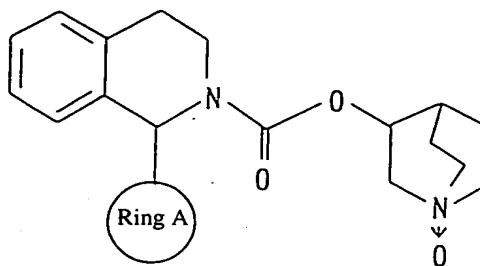
| Compound No. | R _a |
|--------------|----------------|
| B-188 | |
| B-189 | |
| B-190 | |

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T840X

Table 33



| Compound No. | Ring A | Compound No. | Ring A |
|--------------|--------|--------------|--------|
| B - 191 | | B - 196 | |
| B - 192 | | B - 197 | |
| B - 193 | | B - 198 | |
| B - 194 | | B - 199 | |
| B - 195 | | | |

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